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1,4-Dichlorobenzene – Addendum for evaluation of BAT value, BAR and EKA

Assessment Values in Biological Material – Translation of the German version from 2020

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1,4-dichlorobenzene, biological tolerance value, BAT value, biological reference value, BAR, exposure equivalents for carcinogenic substances, EKA, biomonitoring, 2,5-dichlorophenol

Abstract

In 2019, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has derived a biological tolerance value (BAT value) and a biological reference value (BAR) and has re-evaluated the exposure equivalents for carcinogenic substances (EKA) for 1,4-dichlorobenzene [106-46-7].

Based on the available studies on the correlation between external and internal exposure of 1,4-dichlorobenzene in the air and its metabolite 2,5-dichlorophenol in urine, the EKA correlation was slightly modified and extended to the lower concentration range.

In correlation to the maximum concentration at the workplace (MAK value) of 2 ml 1,4-dichlorobenzene/m^3 a BAT value of 10 mg 2,5-dichlorophenol/l urine was derived. For long-term exposure the sampling time is at the end of the shift after several shifts.

According to the different use of 1,4-dichlorobenzene as deodorant and insecticide in various countries, the German study with urine samples of 692 adults was considered for the evaluation of a BAR of 25 µg 2,5-dichlorophenol/l urine.

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BAT value (2019)	**10 mg 2,5-dichlorophenol (after hydrolysis)/l urine**
BAR (2019)	**25 µg 2,5-dichlorophenol (after hydrolysis)/l urine**
EKA (2019)	The following correlation between external and internal exposure is obtained:

Air 1,4-Dichlorobenzene		**Urine 2,5-Dichlorophenol (after hydrolysis)**
[ml/m³]	**[mg/m³]**	**[mg/l]**
2	12	10
5	30,5	20
10	61	30
20	122	60
30	183	90

Sampling time: end of exposure or end of the shift; for long-term exposures: end of the shift after several previous shifts

MAK value (2017)	**2 ml/m³ (ppm) ≙ 12 mg/m³**
Absorption through the skin (2001)	H
Sensitization	–
Carcinogenicity (2017)	Category 4
Prenatal toxicity (2017)	Pregnancy Risk Group C
Germ cell mutagenicity	–

1,4-Dichlorobenzene was re-evaluated by the Commission in 2017 (translated in Hartwig and MAK Commission 2019) based on the data compilations in the EU Risk Assessment Report (EU 2004) and by SCOEL (European Commission 2014). According to these data, 1,4-dichlorobenzene induces malignant liver tumours in mice via cytotoxic and mitogenic mechanisms; genotoxicity is not the main effect. Therefore, 1,4-dichlorobenzene was classified in Carcinogen Category 4.

The most sensitive toxicity end point of 1,4-Dichlorbenzol is hepatocellular hypertrophy in dogs after 52-week oral exposure. From the NAEL (no adverse effect level) of 5 mg/kg body weight and day a MAK value of 2 ml/m³ has been derived (Hartwig and MAK Commission 2019).

In this Addendum, biological exposure equivalents for carcinogenic substances (EKA), evaluated in 2006 (translated in Leng and Lewalter 2010), are re-evaluated and a biological tolerance value (BAT value) and a biological reference value (BAR) are derived.

Re-evaluation of the EKA

In occupationally exposed workers, Pagnotto and Walkley (1965) determined the concentrations of 1,4-dichlorobenzene in the air and of 2,5-dichlorophenol in urine. The concentration in urine was determined after hydrolysis by colorimetry, which makes it difficult to distinguish between differently substituted dichlorophenols. However, in contrast to the general population, workers in the environmental studies were exposed only to 1,4-dichlorobenzene, whose main metabolite is 2,5-dichlorophenol. The following relationship between external and internal exposure was obtained:

$$\text{2,5-dichlorophenol in urine (mg/l)} = 2.8 \times \text{1,4-dichlorobenzene in air (ml/m}^3\text{)} + 3.16\ (R^2 = 0.84).$$

Ghittori et al. (1985) determined the pre- and post-shift values of 2,5-dichlorophenol in the urine of 4 workers occupationally exposed to 1,4-dichlorobenzene during a working week. The difference was related to the air concentration of 1,4-dichlorobenzene. Since the urine samples were not hydrolysed before analysis and only four people were examined, this study is not used to derive the EKA.

In the study by Yoshida et al. (2002), the air concentrations of 1,4-dichlorobenzene in a collective of 119 non-occupationally exposed persons were determined by personal air measurements and the concentrations of 2,5-dichlorophenol in urine. At a median background exposure of 2.5 µl 1,4-dichlorobenzene/m^3 (max. 33.3 µl/m^3, nearly equal to 198 µg/m^3 at 25 ℃), the median concentration of the metabolite in urine was 0.45 mg 2,5-dichlorophenol/l (0.39 mg/g creatinine). Thus, the concentrations in the air are significantly lower than the concentrations at the workplace, which are 25–487 mg 1,4-dichlorobenzene/m^3 (IARC 1999). The relationship between air and urinary concentration was given with the equation 2,5-dichlorophenol (mg/g creatinine) = 0.08 × 1,4-dichlorobenzene in the air (µl/m^3) + 0.181 (r = 0.811). Since the air concentrations measured in this study are significantly lower than those measured at workplaces with 1,4-dichlorobenzene exposure (µg/m^3 instead of mg/m^3), they are not suitable for deriving a correlation for a significantly higher exposure range. The study is therefore not taken into account when determining the EKA correlation.

Table 1 shows the exposure data used for the derivation of the EKA correlation.

Tab. 1 Data on internal and external exposure at different workplaces (Pagnotto and Walkley 1965)

	1,4-Dichlorobenzene in air [ml/m^3]	2,5-Dichlorophenol in urine[a] [mg/l]
1,4-Dichlorobenzene manufacturing		
Washing	34 (7–48)	91 (64–141)
Shoveling and centrifuging	33 (10–49)	103 (54–233)
Crushing and sizing	24 (8–46)	75 (35–165)
Household product packaging		
Pulverizing	25 (18–34)	70 (53–87)
Moth cake line	11 (8–12)	30 (20–38)
Dumping crystals	9 (7–10)	20 (20)
Crystal line	11 (8–18)	14 (10–17)
Abrasive manufacturing		
Mixing	11.5 (8–14.5)	60 (45–68)
Wheel-forming	8 (7–9)	33 (26–43)

[a] adjusted to a specific gravity of 1.024

Table 2 shows the correlation between 1,4-dichlorobenzene in the air and 2,5-dichlorophenol in urine resulting from the regression equation of Pagnotto and Walkley (1965).

Tab. 2 Correlation between 1,4-dichlorobenzene (1,4-DCB) in air and 2,5-dichlorophenol (2,5-DCP) in urine (Pagnotto and Walkley 1965)

Regression equation	Coefficient of determination R^2	Correlation	
		air [ml/m³]	urine [mg/l]
2,5-DCP (mg/l) = 2.8 × 1,4-DCB (ml/m³) + 3.16	0.84	2	9
		5	17
		10	31
		20	59
		30	87

Based on the reevaluated data, the following EKA correlation (Table 3) between external and internal exposure is established:

Tab. 3 EKA correlation for 1,4-dichlorobenzene

Air 1,4-Dichlorobenzene		Urine 2,5-Dichlorophenol (after hydrolysis)
[ml/m³]	[mg/m³]	[mg/l]
2	12	10
5	30.5	20
10	61	30
20	122	60
30	183	90

Since the 2,5-dichlorophenol concentrations used to derive the EKA correlation were given in mg/l urine, this unit is also used to derive the EKA correlation.

Evaluation of a BAT value

Using the EKA correlation, from an air concentration at the level of the MAK value of 2 ml 1,4-dichlorobenzene/m³

a BAT-value of 10 mg 2,5-dichlorophenol (after hydrolysis)/l urine

is derived. Sampling time should be at the end of exposure or at the end of the shift; for long term exposures at the end of the shift after several previous shifts.

Evaluation of a BAR

Studies on background exposure to 1,4-dichlorobenzene leading to 2,5-dichlorophenol excretion are listed in Table 4. The exposure of the general population in Japan (Yoshida et al. 2002) is significantly higher than in Germany, which is partly due to the increased use of toilet cleaning products (toilet blocks). In Germany, Angerer et al. (1992) determined the sum of 2,4- and 2,5-dichlorophenol in the urine of 258 men and women with a 95th percentile of 33.6 µg/l. In the study by Schmid et al. (1997) a 95th percentile for 2,5-dichlorophenol in urine of 14.74 µg/l was given. In the environmental survey by Becker et al. (2003) the chlorophenol exposure was investigated in a representative population study of 692 persons between 18 and 69 years of age and a 95th percentile of 27 µg/l was determined for 2,5-dichlorophenol in urine.

Tab. 4 Concentrations of 2,5-dichlorophenol in the urine of the general population

Country, collective	2,5-Dichlorophenol in urine [µg/l]	References
Japan		
n = 119 ♂, ♀ age: 21–83 years	median: 450 range (60–3730)	Yoshida et al. 2002
Germany		
n = 258 ♂, ♀	95^{th} percentile: 33.6 (2,4- + 2,5-dichlorophenol) range (< 0.6–209)	Angerer et al. 1992
n = 33 ♂ age: 25–36 years	95^{th} percentile: 14.74 range (0.45–18.93)	Schmid et al. 1997
n = 692 ♂, ♀ age: 18–69 years	95^{th} percentile: 27 maximum value 1550	Becker et al. 2003

The biological reference value (BAR) is derived from the data obtained in Germany by Becker et al. (2003) to account for possible regional influence factors. Based on this study,

a BAR of 25 µg 2,5-dichlorophenol (after hydrolysis)/l urine

has been derived.

Sampling time is at the end of exposure or at the end of the shift; for long term exposures at the end of the shift after several previous shifts.

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